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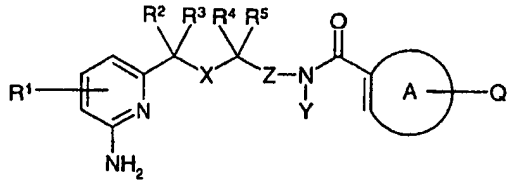


(I)

(57) Abstract

There are provided novel compounds of formula (I), wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, A, Q, X, Y and Z are defined in the specification, and pharmaceutically acceptable salts thereof, and enantiomers and tautomers thereof; together with processes for their preparation, compositions containing them and their use in therapy. The compounds are inhibitors of the enzyme nitric oxide synthase and are thereby particularly useful in the treatment of prophylaxis of inflammatory disease and pain.

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# COMPOUNDS

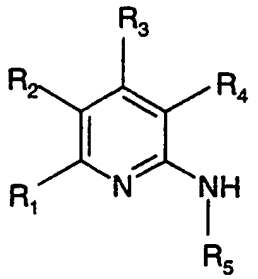
## Field of the Invention

The present invention relates to novel 2-aminopyridine derivatives, processes for their preparation, compositions containing them and their use in therapy.

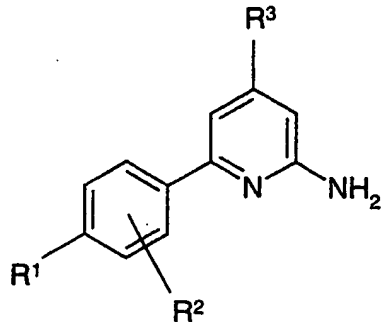
## Background of the Invention

Nitric oxide is produced in mammalian cells from L-arginine by the action of specific nitric oxide synthases (NOSs). These enzymes fall into two distinct classes - constitutive NOS (cNOS) and inducible NOS (iNOS). At the present time, two constitutive NOSs and one inducible NOS have been identified. Of the constitutive NOSs, an endothelial enzyme (ecNOS) is involved with smooth muscle relaxation and the regulation of blood pressure and blood flow, whereas the neuronal enzyme (ncNOS) serves as a neurotransmitter and appears to be involved in the regulation of various biological functions such as cerebral ischaemia. Inducible NOS has been particularly implicated in the pathogenesis of inflammatory diseases. Regulation of these enzymes should therefore offer considerable potential in the treatment of a wide variety of disease states (J. E. Macdonald, *Ann. Rep. Med. Chem.*, 1996, **31**, 221 - 230).

Considerable effort has been expended in efforts to identify compounds that act as specific inhibitors of one or more isoforms of the enzyme nitric oxide synthase. The use of such compounds in therapy has also been widely claimed. One group of these compounds incorporates within their structures a 2-aminopyridine moiety. Thus, WO 96/18616 and WO 96/18617 (both to Merck & Co., Inc.) describe substituted 2-aminopyridines of general formula:



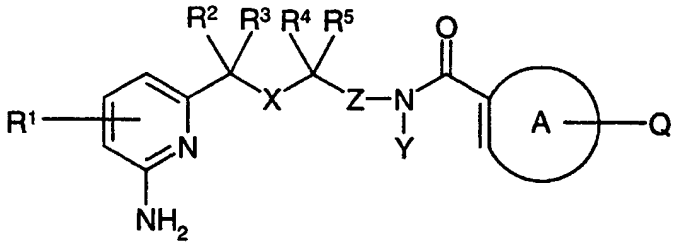
and WO 97/36871 (Pfizer Inc.) describes 6-phenyl-2-aminopyridines of general formula:



The compounds of the present invention are clearly distinguished from those of the prior art by virtue of the nature of the particular substituents attached to the 2-aminopyridine ring.

Disclosure of the invention

According to the present invention, there is provided a compound of formula (I)



(I)

wherein:

X represents $-[CR^6R^7]_n-$;

$R^1$ represents hydrogen or one or more substituents selected independently from C1 to 6 alkyl, C1 to 6 alkoxy, halogen and $NR^8R^9$;

$R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ independently represent hydrogen or C1 to 4 alkyl;

or $R^2$ and $R^4$ are joined together and represent $-[CH_2]_m-$;

Y represents hydrogen or C1 to 4 alkyl;

or $R^2$ and Y are joined together and represent $-[CH_2]_p-$;

or $R^4$ and Y are joined together and represent $-[CH_2]_p-$;

or Y is joined to the ortho position of ring A and represents $-[CH_2]_r-$;

Z represents a bond or $-CH_2-$;

Q represents hydrogen, C1 to 6 alkyl, C1 to 6 alkoxy, C1 to 6 alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, hydroxy, nitro, methanesulphonyl, sulphamoyl, benzyloxy, $-NR^8R^9$, $-CO_2R^{10}$ or $-CONR^{11}R^{12}$;

$R^{10}$, $R^{11}$ and $R^{12}$ independently represent hydrogen or C1 to 4 alkyl;

A represents phenyl, a five membered aromatic heterocyclic ring containing one or two heteroatoms selected independently from O, S or N, or a six membered aromatic azacyclic ring containing one or two nitrogen atoms;

m represents an integer 0 to 5;

n represents an integer 0 to 3;

p represents an integer 0 to 4;

r represents an integer 0 to 3;

or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers have the advantage that they are inhibitors of the enzyme nitric oxide synthase (NOS). In particular, the compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers have the advantage that they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase (iNOS).

The invention further provides a process for the preparation of compounds of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

According to the invention there is also provided a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, for use as a medicament.

Another aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

A more particular aspect of the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

According to the invention, there is also provided a method of treating, or reducing the risk of, diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering to a person suffering from or at risk of, said disease or condition, a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

More particularly, there is also provided a method of treating, or reducing the risk of, inflammatory disease in a person suffering from or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

The compounds of the present invention may also be used advantageously in combination with a second pharmaceutically active substance, particularly in combination with a selective inhibitor of the inducible isoform of cyclooxygenase (COX-2). Thus, in a further aspect of the invention there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof, in combination with a COX-2 inhibitor for the treatment of inflammation, inflammatory disease and inflammatory related disorders. And there is also provided a method of treating, or reducing the risk of, inflammation, inflammatory disease and inflammatory related disorders in a person suffering from or at risk of, said disease or condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof in combination with a COX-2 inhibitor.

Preferably, A in formula (I) represents a phenyl or pyridyl ring.

Preferably, Q in formula (I) represents hydrogen, halogen or cyano.

Preferably, $R^1$ in formula (I) represents C1 to 6 alkyl or C1 to 6 alkoxy. More preferably, $R^1$ in formula (I) represents methyl or methoxy.

Preferably, n in formula (I) represents 0 or1.

Particular compounds of the invention include:

N-[4-(6-amino-4-methyl-2-pyridinyl)ethyl]-4-cyanobenzamide;

N-[4-(6-amino-4-methyl-2-pyridinyl)butyl]-4-cyanobenzamide;
N-[4-(6-amino-4-methyl-2-pyridinyl)ethyl]-4-chlorobenzamide;
2-[2-(6-amino-4-methyl-2-pyridinyl)ethyl]-5-bromo-2,3-dihydro-1H-isoindol-1-one;
N-[2-(6-amino-4-methyl-2-pyridinyl)ethyl]-4-cyano-N-methylbenzamide;
N-[2-(6-amino-4-methyl-2-pyridinyl)ethyl]-N-methyl-2-furanocarboxamide;
N-[2-(6-amino-4-methyl-2-pyridinyl)ethyl]-4-chloro-N-methylbenzamide;
N-[3-(6-amino-4-methyl-2-pyridinyl)propyl]-4-chlorobenzamide;
4-methyl-6-(4-(1-(4-chlorobenzoyl)piperidinyl)-2-pyridinamine;
and pharmaceutically acceptable salts, enantiomers, racemates or tautomers thereof.

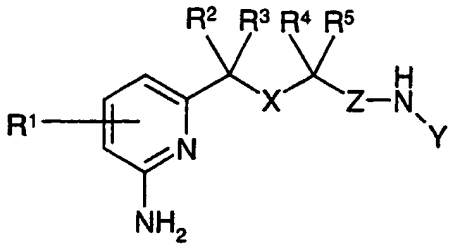
Unless otherwise indicated, the term "C1 to 6 alkyl " referred to herein denotes a straight or branched chain alkyl group having from 1 to 6 carbon atoms or a cyclic alkyl group having from 3 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, cyclopentyl and cyclohexyl.

Unless otherwise indicated, the term "C1 to 6 alkoxy " referred to herein denotes a straight or branched chain alkoxy group having from 1 to 6 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy and t-butoxy.

Other groups, for example, alkylthio, are to be interpreted similarly.

Examples of a five membered aromatic heterocyclic ring containing one or two heteroatoms selected independently from O, S or N, or a six membered aromatic azacyclic ring containing one or two nitrogen atoms include furan, thiophene, pyrrole, thiazole, oxazole, imidazole, pyridine, pyrimidine, pyrazine and pyridazine.

The process mentioned above, for the preparation of compounds of the invention, or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof comprises reaction of a compound of formula (II)

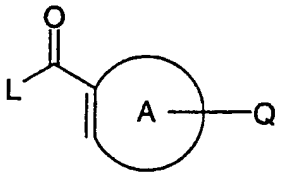


(II)

wherein

$R^1$, $R^2$, $R^3$, $R^4$, $R^5$, X, Y and Z are as defined above

with an acyl derivative of formula (III)



(III)

wherein

Q and A are as defined above and L represents a leaving group;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or *vice versa*, and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

The reaction process will take place on stirring a mixture of the reactants in a suitable organic solvent at a suitable temperature, generally between 0 °C and the boiling point of the solvent. The reaction time will depend *inter alia* on the solvent used, the reaction temperature and the nature of the group L. The reaction may be catalysed by the addition of a base; bases that may be used include organic amines (for example, triethylamine or pyridine) and alkali metal hydroxides, alkoxides, carbonates or hydrides. Suitable leaving groups, L, include halogen (especially chlorine) and hydroxyl. When L represents OH, the reaction between compounds of formulae (II) and (III) may also be achieved using a suitable coupling agent such as CDI (1,1′-carbonyldiimidazole) , DCC (1,3-dicyclohexylcarbodiimide) or HOBt (1-hydroxybenzotriazole).

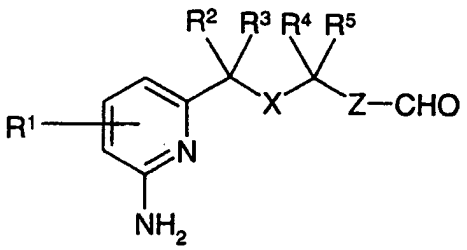
It will be apparent to a person skilled in the art that in the above process it may be desirable to protect an amine or other potentially reactive group. Suitable protecting groups and details of processes for adding and removing such groups may be found by reference to the standard text "Protecting Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts.

The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

Salts of compounds of formula (I) may be formed by reacting the free base, or a salt, enantiomer, racemate or tautomer thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble or in a solvent in which the salt is soluble, for example, water, dioxane, ethanol, tetrahydrofuran or diethyl ether, or a mixture of solvents, which may be removed *in vacuo* or by freeze drying. The reaction may also be a metathetical process or it may be carried out on an ion exchange resin.

Certain novel intermediates of formulae (II) and (III) form another aspect of the invention.

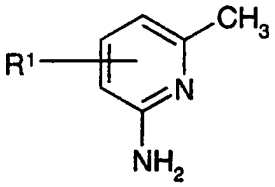
Compounds of formula (II) may be prepared by reductive amination of a compound of formula (IV)




(IV)

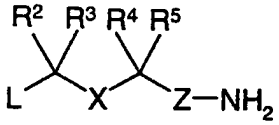
using procedures that are well known in the art. When carrying out such reactions, it will generally be advantageous to protect the amino group on the pyridyl ring.

Alternatively, compounds of formula (II) may be prepared by metallation of a compound of formula (V)




(V)

using a suitable base such as butyl lithium or lithium diisopropylamide, followed by reaction of the metallated derivative with a compound of formula (VI) or a protected derivative thereof.




(VI)

wherein L is a suitable leaving group such as halide.

Methods for the preparation of compounds of formulae (III), (IV), (V) and (VI) are either known *per se* or may be achieved using methods that are well known in the art.

Intermediate compounds may be used in protected form. Protecting groups and details of processes for their removal may be found by reference to the standard text "Protecting Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts.

The compounds of the invention and intermediates thereto may be isolated from their reaction mixtures and, if necessary further purified, by using standard techniques.

The compounds of formula I may exist in enantiomeric forms. Therefore, all enantiomers, diastereomers, racemates and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation, or HPLC.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures.

The compounds of formula (I) may exist in alternative tautomeric forms. Compounds of formula (I) are provided in another tautomeric form or as a mixture thereof.

The compounds of formula (I), and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers, are useful because they possess pharmacological activity in animals. In particular, the compounds are active as inhibitors of the enzyme nitric oxide synthase. More particularly, they are inhibitors of the inducible isoform of the enzyme nitric oxide synthase and as such are predicted to be useful in therapy, for example, as anti-inflammatory agents. They may also have utility as inhibitors of the neuronal isoform of the enzyme nitric oxide synthase.

The compounds and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers are indicated for use in the treatment or prophylaxis of diseases or conditions in which synthesis or oversynthesis of nitric oxide synthase forms a contributory part. In particular, the compounds are indicated for use in the treatment of inflammatory conditions in mammals including man.

Conditions that may be specifically mentioned are:
osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis and other arthritic conditions, inflamed joints;
eczema, psoriasis, dermatitis or other inflammatory skin conditions such as sunburn;
inflammatory eye conditions including uveitis and conjunctivitis;

lung disorders in which inflammation is involved, for example, asthma, bronchitis, chronic obstructive pulmonary disease, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome;

bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, pain, meningitis and pancreatitis;

conditions of the gastrointestinal tract including inflammatory bowel disease, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, irritable bowel syndrome, damage to the gastrointestinal tract resulting from infections by, for example, *Helicobacter pylori*, or from treatments with non-steroidal anti-inflammatory drugs;

and other conditions associated with inflammation.

The compounds will also be useful in the treatment and alleviation of acute pain or persistent inflammatory pain or neuropathic pain or pain of a central origin.

We are particularly interested in the conditions inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, chronic obstructive pulmonary disease and pain.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers may also be useful in the treatment or prophylaxis of diseases or conditions in addition to those mentioned above. For example, the compounds may be useful in the treatment of atherosclerosis, glaucoma, cystic fibrosis, hypotension associated with septic and/or toxic shock, in the treatment of dysfunction of the immune system, as an adjuvant to short-term immunosuppression in organ transplant therapy, in the control of onset of diabetes, in the maintenance of pancreatic function in diabetes, in the treatment of vascular complications associated with diabetes and in cotherapy with cytokines, for example TNF or interleukins.

The compounds of formula (I) may also be useful in the treatment of hypoxia, for example in cases of cardiac arrest and stroke, neurodegenerative disorders including nerve degeneration and/or nerve necrosis in disorders such as ischaemia, hypoxia, hypoglycaemia, epilepsy, and in external wounds (such as spinal cord and head injury), hyperbaric oxygen convulsions and

toxicity, dementia, for example pre-senile dementia, Alzheimer's disease and AIDS-related dementia, Sydenham's chorea, Parkinson's disease, Tourette's Syndrome, Huntington's disease, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, depression, pain, autism, seasonal affective disorder, jet-lag, depression or other symptoms associated with Premenstrual Syndrome (PMS), anxiety and septic shock. Compounds of formula (I) may also be expected to show activity in the prevention and reversal of tolerance to opiates and diazepines, treatment of drug addiction, treatment of migraine and other vascular headaches, neurogenic inflammation, in the treatment of gastrointestinal motility disorders, cancer and in the induction of labour.

We are particularly interested in the conditions stroke, Alzheimer's disease, Parkinson's disease, multiple sclerosis, schizophrenia, migraine, cancer, septic shock and pain.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

For the above mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered at a dosage of the solid form of between 1 mg and 2000 mg per day.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may be used on their own, or in the form of appropriate pharmaceutical compositions in which the compound or derivative is in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. Administration may be by, but is not limited to, enteral (including oral, sublingual or rectal), intranasal, intravenous, topical or other parenteral routes. Conventional procedures for the selection and preparation of suitable pharmaceutical

formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988. The pharmaceutical composition preferably comprises less than 80% and more preferably less than 50% of a compound of formula (I), or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

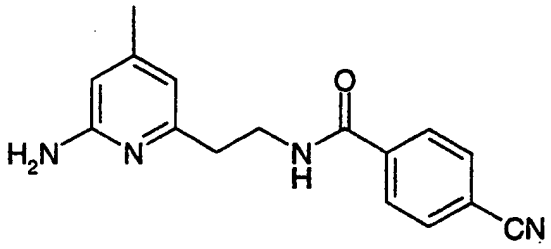
There is also provided a process for the preparation of such a pharmaceutical composition that comprises mixing the ingredients.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may also be advantageously used in combination with a COX-2 inhibitor. Particularly preferred COX-2 inhibitors are Celecoxib and MK-966. The NOS inhibitor and the COX-2 inhibitor may either be formulated together within the same pharmaceutical composition for administration in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

The invention is illustrated, but in no way limited, by the following examples:

## Example 1

N-[4-(6-Amino-4-methyl-2-pyridinyl)ethyl]-4-cyanobenzamide hydrochloride




(a) 2-(2-Azidoethyl)-6-(2,5-dimethyl-1-*H*-pyrrol-1-yl)-4-methylpyridine

A solution of 6-(2,5-dimethyl-1*H*-pyrrol-1-yl)-4-methyl-2-pyridineethanol methanesulfonate (0.81 g, 2.63 mmol) in dry N,N-dimethylformamide (5 ml) was treated

with sodium azide (341 mg, 5.25 mmol). The mixture was stirred at ambient temperature for three days and then diluted with water (30 ml). The products were extracted into ether (3 x 50 ml) and the extracts dried ($MgSO_4$) and concentrated to afford an oil. The crude material was purified on silica gel by flash column chromatography using ether - isohexane 1:1 as eluent to give the title compound (490 mg, 73%).

MS APCI +ve $^{m}/z$ 256 ($[M+H]^+$), 228 (100%).

(b) 6-(2-Azidoethyl)-4-methyl-2-pyridinamine

2-(2-Azidoethyl)-6-(2,5-dimethyl-1-*H*-pyrrol-1-yl)-4-methylpyridine (490 mg, 1.92 mmol) in ethanol was treated with hydroxylamine hydrochloride (615 mg, 0.88 mmol) and aqueous potassium hydroxide (300 mg, 5.4 mmol in 3 ml water). The mixture was then heated under reflux for 36h. The mixture was concentrated, and the residue partitioned between 10% aqueous potassium hydroxide (20 ml) and ethyl acetate (50 ml). The organic extract was collected and dried ($MgSO_4$). Concentration of the extract afforded an oil which was purified on silica gel by flash column chromatography using 80% ethyl acetate - isohexane as eluent. The title compound was isolated as a colourless oil (270 mg, 79%).

MS APCI +ve $^{m}/z$ 178 ($[M+H]^+$)

(c) N-[4-(6-Amino-4-methyl-2-pyridinyl)ethyl]-4-cyanobenzamide hydrochloride

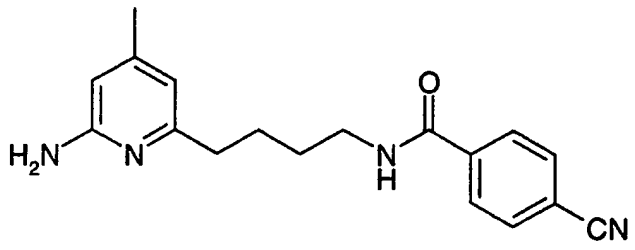
A solution of 6-(2-azidoethyl)-4-methyl-2-pyridinamine (270 mg, 1.53 mmol) in dry tetrahydrofuran (20 ml) was treated with triphenylphosphine (400 mg, 1.53 mmol). The mixture was heated under reflux for 17h. Water (0.04 ml, 1.5 equivalents) was added to the mixture, and heating continued for 1h. The solvent was removed under vacuo, and the residue dissolved in acetonitrile (20 ml). To the stirred mixture was added triethylamine (0.22 ml, 3 mmol) and 4-cyanobenzoyl chloride (253 mg, 1.53 mmol). After 1h the mixture was evaporated and the residue triturated with a small amount of acetonitrile to afford a colourless solid. The crude product was dissolved in methanol (5 ml) and the solution treated with ethereal hydrogen chloride. The title compound was isolated as a colourless solid (230 mg, 48%).

MS APCI +ve $^{m}/z$ 281 ($[M+H]^+$);

300 MHz $^1$H NMR ($d_6$-DMSO) 14.05 (1H, br s), 8.98 (1H, t, J 5.4Hz), 7.96 (4H, s), 7.76 (2H, br s), 6.62 (1H, s), 6.58 (1H, s), 3.64 (2H, q, J 6.3Hz), 2.93 (2H,t, J 6.6Hz), 2.24 (3H, s).

## Example 2

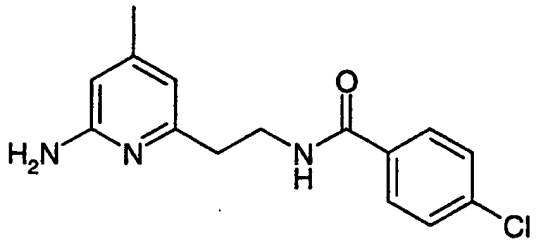
N-[4-(6-Amino-4-methyl-2-pyridinyl)butyl]-4-cyanobenzamide




6-(4-Aminobutyl)-4-methyl-2-pyridinamine dihydrochloride (100 mg) was stirred in acetonitrile (20 ml) and treated with 4-cyanobenzoyl chloride (73 mg) followed by triethylamine (0.17 ml). The reaction mixture was stirred for 24 h, diluted with water, extracted with ethyl acetate, the combined extracts washed with sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated. The residue was dissolved in ethanol and treated with 1N hydrochloric acid in ether, then evaporated. The residue was dissolved in water, washed with dichloromethane and basified with 40% sodium hydroxide solution. The basic solution was extracted with ethyl acetate, the extract washed with brine, dried over magnesium sulphate and evaporated to give a colourless solid (59 mg), m.p. 138-139 °C;
MS (+CI) $^m/z$ 309 ($[M+H]^+$);
300 MHz $^1$H NMR ($CDCl_3$) 7.87 (2H, d), 7.65 (2H, d), 7.12 (1H, br.s), 6.31 (1H, s), 6.11 (1H, s), 4.18 (2H, br.s), 3.44 (2H, m), 2.59 (2H, t), 2.14 (3H, s), 1.73 (2H, m), 1.63 (2H, m).

## Example 3

N-[4-(6-Amino-4-methyl-2-pyridinyl)ethyl]-4-chlorobenzamide



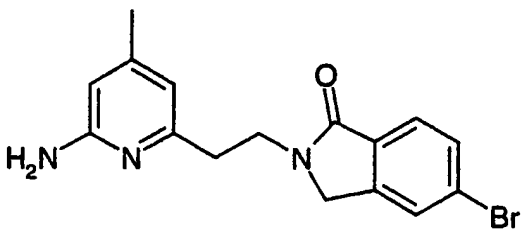
4-Chlorobenzoic acid (87 mg, 0.558 mmol) in dry N,N-dimethylformamide (3 ml) was treated with 1,1-carbonyldiimidazole (90 mg, 0.558 mmol) and stirred for 1h. 6-(2-Aminoethyl)-4-methyl-2-pyridinamine (100 mg, 0.558 mmol) prepared as in Example 1(c) was dissolved in dry N,N-dimethylformamide (3 ml) and added to the above reaction mixture which was stirred for 3h. The solvent was removed by evaporation and the residue dissolved in ethyl acetate (50 ml) washed with water (6 x 50 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue triturated with isohexane/diethyl ether to give the title compound (97 mg, 60%) as a cream coloured solid.

MS APCI +ve $^{m}/z$ 290($[M+H]^+$);

$^1H$ NMR 300 MHz ($d_6$-DMSO) 7.66 (2H, d), 7.32 (2H, d), 6.34 (1H, s), 6.15 (1H, s), 4.24 (2H, br s), 3.68 (2H, q), 2.78 (2H, t), 2.14 (3H, s).

## Example 4

2-[2-(6-Amino-4-methyl-2-pyridinyl)ethyl]-5-bromo-2,3-dihydro-1H-isoindol-1-one



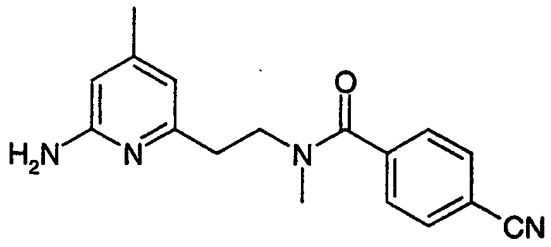
6-(2-Aminoethyl)-4-methyl-2-pyridinamine (111 mg, 0.738 mmol) prepared as in Example 1(c) and methyl 4-bromo-2-bromomethylbenzoate (227 mg, 0.738 mmol) in acetonitrile (5 ml) was treated with triethylamine (0.35 ml, 2.48 mmol) and the mixture heated under reflux for 2h. The reaction mixture was cooled, diluted with water (50 ml) and ethyl acetate (50 ml), the organic layer was separated washed with water (50 ml) then brine and dried ($MgSO_4$). The solvent was evaporated and the residue eluted down a flash chromatography column using initially 10% isohexane/ethyl acetate, then ethyl acetate and finally 10% methanol/ethyl acetate. The product obtained on evaporation was triturated with ether to give the title compound (108 mg, 42%) as a colourless solid.

MS APCI +ve $^{m}/z$ 346/348($[M+H]^+$);

$^1$H NMR 300 MHz ($d_6$-DMSO) 7.84 (1H, d), 7.66 (1H, d of d), 7.59 (1H, d), 6.24 (1H, s), 6.10 (1H, s), 5.74 (2H, brs), 4.43 (2H, s), 3.77 (2H, t), 2.75 (2H, t), 2.07 (3H, s).

## Example 5

N-[2-(6-Amino-4-methyl-2-pyridinyl)ethyl]-4-cyano-N-methylbenzamide



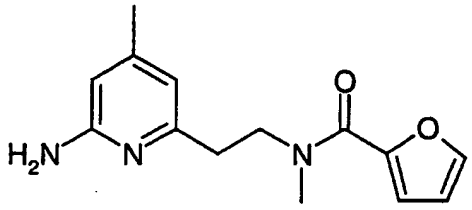

Prepared as the method of Example 2 using 6-(2-N-methylaminoethyl)-4-methyl-2-pyridinamine and p-cyanobenzoyl chloride to give the product as a crystalline solid.

MS APCI +ve $^{m}/z$ 295 ($[M+H]^+$);

$^1$H NMR 300 MHz ($d_6$-DMSO) 7.92-7.27 (4H, m), 6.29-5.63 (4H, m),3.71-3.4 (2H, m), 2.99-2.63 (5H, m), 2.11-2.07 (3H, 2xs).

## Example 6

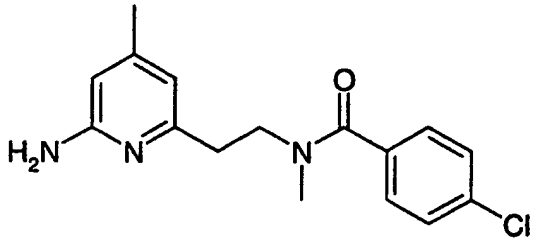
N-[2-(6-Amino-4-methyl-2-pyridinyl)ethyl]-N-methyl-2-furanocarboxamide



Prepared according to the method of Example 2 using 6-(2-N-methylaminoethyl)-4-methyl-2-pyridinamine and 2-furoyl chloride to give the product as a solid.
MS APCI +ve $^{m}/z$ 260 ($[M+H]^+$);
$^1$H NMR 300 MHz ($d_6$-DMSO) 7.7 (1H, d), 6.92 (1H, d), 6.55 (1H, m), 6.22 (1H, s), 6.12 (1H, s), 5.39 (2H, brs), 3.74 (2H, m), 2.75 (2H, m), 2.09 (3H, s).

Example 7

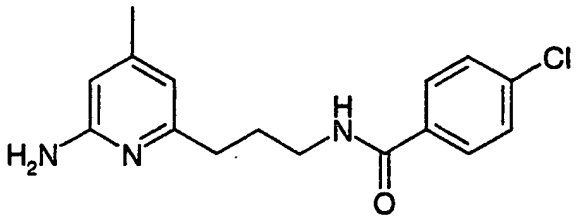
N-[2-(6-Amino-4-methyl-2-pyridinyl)ethyl]-4-chloro-N-methylbenzamide



Prepared according to the method of Example 3 using 6-(2-N-methylaminoethyl)-4-methyl-2-pyridinamine and 4-chlorobenzoic acid to give the product as a pale yellow solid.
MS APCI +ve $^{m}/z$ 304 ($[M+H]^+$);
$^1$H NMR 300 MHz ($d_6$-DMSO) 7.45-7.26 (4H, m), 6.18 (1H, s), 6.13 (1H, s), 5.39 (2H, brs), 3.58 (2H, t), 2.89 (3H, s), 2.7 (2H, t), 2.09 (3H, s).

Example 8

N-[3-(6-Amino-4-methyl-2-pyridinyl)propyl]-4-chlorobenzamide



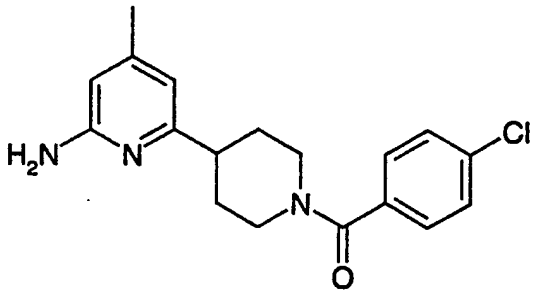
Prepared according to the method of Example 3 using 6-(3-aminopropyl)-4-methyl-2-pyridinamine hydrochloride and 4-chlorobenzoic acid to give the product as a cream coloured solid.

MS APCI +ve $^{m}/z$ 304([M+H]$^{+}$);

$^{1}$H NMR 300 MHz ($d_6$-DMSO) 8.59 (1H, br m), 7.86 (2H, d of d), 7.53 (2H, d of d), 6.50 (1H, s), 6.44 (1H, s), 3.28 (2H, m), 2.67 (2H, m), 2.23 (3H, s), 1.88 (2H, m).

Example 9

4-Methyl-6-(4-(1-(4-chlorobenzoyl)piperidinyl)-2-pyridinamine



(a) N-(6-Bromo-4-methyl-2-pyridinyl)acetamide

6-Bromo-4-methyl-2-pyridinamine (2.12 g, 11.3 mmol) was heated under reflux in acetic anhydride (50 ml) for 1h. The reaction mixture was cooled and poured onto ice/water and

left to stand for 1h. The solid was collected by filtration, washed well with water and extracted into ethyl acetate (150 ml) which was washed with water (100 ml), aqueous sodium bicarbonate then brine and dried ($MgSO_4$). The solvent was evaporated to give the required product (1.61 g, 62%) as a light brown solid.

MS APCI +ve $^m/z$ 228/230($[M+H]^+$).

(b) N-[6-(1-Acetyl-1,2,3,6-tetrahydro-4-pyridinyl)-4-methyl-2-pyridinyl]acetamide

To N-(6-Bromo-4-methyl-2-pyridinyl)acetamide (1.32 g, 5.74 mmol) in dry dimethylformamide (30 ml) previously purged with nitrogen gas was added 1-[4-(tributylstannyl)-3-cyclohexen-1-yl]-1-ethanone (2.45 g, 5.92 mmol), bis(triphenylphosphine)palladium (II) chloride (81 mg, 0.115 mmol) and 2,6-dibutyl-4-methylphenol (5 crystals) and the mixture heated and stirred under reflux for 4h. The solvent was evaporated, the residue dissolved in dichloromethane, filtered and the filtrate eluted down a flash chromatography column using 5% methanol/dichloromethane to give the product (600 mg, 38%) as a cream solid.

MS APCI +ve $^m/z$ 274 ($[M+H]^+$).

(c) 4-Methyl-6-(1,2,3,6-tetrahydro-4-pyridinyl)-2-pyridinamine

The above bisamide (590 mg, 2.16 mmol) was heated under reflux in 5N hydrochloric acid (50 ml) for 4h with stirring. After evaporation the residue was azeotroped with dichloromethane (2 x 50 ml), triturated with ether (2 x 50 ml) and finally dissolved in ether and dried over potassium hydroxide pellets. The ether was evaporated to give the required product (450 mg, 100%) as a light brown solid.

$^1H$ NMR 300 MHz ($d_6$-DMSO) 13.8 (1H, br s), 9.43 (2H, br s), 8.25 (2H, br s), 6.92 (1H, s), 6.82 (1H, s), 6.73 (1H, m), 3.84 (2H, m), 3.30 (2H, d), 2.70 (2H, br s), 2.33 (3H, s)

(d) 4-Methyl-6-(4-piperidinyl)-2-pyridinamine

The above tetrahydropyridine (320 mg, 1.69 mmol) was dissolved in absolute ethanol (50 ml) treated with 10% palladium on charcoal (30 mg) and hydrogenated at 3 bar until uptake was complete. The catalyst was filtered off, the filtrate evaporated and the residue

triturated with ether/ isohexane to give the required product (210 mg, 65%) as a cream solid.

MS APCI +ve $^{m}/z$ 192 [$(M+H)^+$];

$^1$H NMR 300 MHz ($d_6$-DMSO) 6.17 (1H, s), 6.06 (1H, s), 5.60 (2H, br s), 2.98 (2H, m), 2.51-2.34 (2H, m), 2.09 (3H, s), 1.71 (2H, m), 1.50 (2H, m).

(e) 4-Methyl–6-(4-(1-(4-chlorobenzoyl)piperidinyl)-2-pyridinamine

Prepared according to the method of Example 3 using 4-methyl-6-(4-piperidinyl)-2-pyridinamine and 4-chlorobenzoic acid to give the title compound (108 mg, 62%) as a colourless foam.

MS APCI +ve $^{m}/z$ 330 ([$(M+H)^+$];

$^1$H NMR 300 MHz ($d_6$-DMSO) 7.51 (2H, d), 7.43 (2H, d), 6.23 (1H, s), 6.10 (1H, s), 5.67 (2H, br s), 4.56 (1H, br s), 3.62 (1H, br s), 3.13 (1H, br s), 2.82 (1H, br s), 2.66 (1H, t), 2.10 (3H, s), 1.83-1.61 (4H, br m).

## Screens

The pharmacological activity of compounds according to the invention was tested in the following screens.

### Screen 1

The activity of compounds of formula (I), or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, may be screened for nitric oxide synthetase inhibiting activity by a procedure based on that of Förstermann *et al.*, Eur. J. Pharm., 1992, **225**, 161-165. Nitric oxide synthase converts $^3$H-L-arginine into $^3$H-L-citrulline which can be separated by cation exchange chromatography and quantified by liquid scintillation counting.

Enzyme is prepared, after induction, from the cultured murine macrophage cell line J774A-1 (obtained from the laboratories of the Imperial Cancer Research Fund). J774A-1 cells are cultured in Dulbeccos Modified Eagles Medium (DMEM) supplemented with 10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 mg/ml

streptomycin & 0.25 mg/ml amphotericin B). Cells are routinely grown in 225 $cm^3$ flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% $CO_2$.

Nitric oxide synthase is produced by cells in response to interferon-g (IFNg) and lipopolysaccharide (LPS). The medium from confluent culture flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 1 mg/ml LPS and 10 units/ml IFNg. After a period of 17-20 hours in culture, harvesting of cells is accomplished by scraping the cell sheet from the flask surface into the culture medium. Cells are collected by centrifugation (1000 g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20 °C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X-100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors comprising leupeptin (2 mg/ml), soya bean trypsin inhibitor (10 mg/ml), aprotinin (5 mg/ml) and phenylmethylsulphonyl fluoride (50 mg/ml).

For the assay, 25 µl of substrate cocktail (50 mM Tris-HCl (pH 7.5 at 20 °C), 400 µM NADPH, 20 µM flavin adenine dinucleotide, 20 µM flavin mononucleotide, 4 µM tetrahydrobiopterin, 12 µM L-arginine and 0.025 mCi L-[$^3$H] arginine) is added to wells of a 96 well filter plate (0.45µM pore size) containing 25 µl of a solution of test compound in 50 mM Tris-HCl. The reaction is started by adding 50 µl of cell lysate (prepared as above) and after incubation for 1 hour at room temperature is terminated by addition of 50 µl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 150 µl of a 25% aqueous slurry of Dowex 50W ($Na^+$ form) is added to the assay after which the whole is filtered into 96 well plates. 75 µl of filtrate is sampled and added to wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75 µl sample which is increased to 1900 dpm in the reagent controls. Compound activity is expressed as $IC_{50}$ (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and aminoguanidine, which

gives an $IC_{50}$ (50% inhibitory concentration) of 10 μM, is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained, $IC_{50}$ values are calculated. Compounds that inhibit the enzyme by at least 25% at 100 μM are classed as being active and are subjected to at least one retest.

In the above screen, the compounds of Examples 1 to 9 were tested and gave $IC_{50}$ values of less than 25 μM indicating that they are expected to show useful therapeutic activity.

Screen 2

Compounds also show activity against the human form of induced nitric oxide synthase as can be demonstrated in the following assay.

Enzyme is prepared, after induction, from the cultured human colon adrenocarcinoma cell line DLD1 (obtained from the European Collection of Animal Cell Culture - cell line number 90102540). DLD1 cells are cultured in RPMI 1640 medium supplemented with 10% foetal bovine serum, 4 mM L-glutamine and antibiotics (100 units/ml penicillin G, 100 μg/ml streptomycin and 0.25 μg/ml amphotericin B). Cells are routinely grown in 225 $cm^3$ flasks containing 35 ml medium kept at 37 °C and in a humidified atmosphere containing 5% $CO_2$.

Nitric oxide synthase is produced by cells in response to interferon-γ (IFN-γ) and interleukin-1β (IL-1β). The medium from confluent flasks is removed and replaced with 25 ml (per flask) of fresh medium containing 250 units/ml IL-1β and 1000 units/ml IFN-γ. After a period of 17–20 hours in culture, harvesting of cells is accomplished by scraping the cell monolayer from the flask surface into the culture medium. Cells are collected by centrifugation (1000g for 10 minutes) and lysate prepared by adding to the cell pellet a solution containing 50 mM Tris-HCl (pH 7.5 at 20°C), 10% (v/v) glycerol, 0.1% (v/v) Triton-X100, 0.1 mM dithiothreitol and a cocktail of protease inhibitors including leupeptin (2 μg/ml), soya bean trypsin inhibitor (10 μg/ml), aprotonin (5 μg/ml) and phenylmethylsulphonyl fluoride (50 μg/ml).

For the assay, 25 µl of substrate cocktail (50 mM Tris-HCl (pH 7.5), 400 µM NADPH, 20 µM flavin adenine dinucleotide, 20 µM flavin mononucleotide and 4 µM tetrahydrobiopterin) is added to the wells of a 96-well plate. Test compounds are preincubated with enzyme by adding together with 40 µl of cell lysate (prepared as above) and incubating for 1 hour at 37 °C at the end of which period 10 µl of 30 µM L-arginine and 0.025 µCi of L-[$^3$H]-arginine in 50 mM Tris-HCl is added to start the enzymatic reaction. Incubation is continued for a further 1 hour at 37 °C. The reaction is terminated by addition of 50 µl of an aqueous solution of 3 mM nitroarginine and 21 mM EDTA.

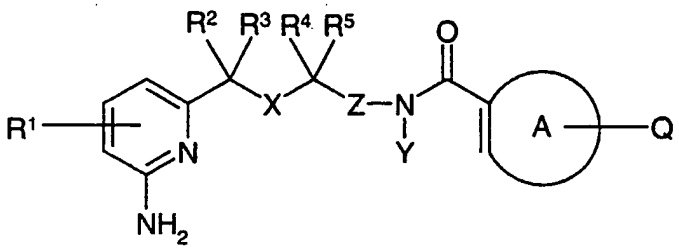
Labelled L-citrulline is separated from labelled L-arginine using Dowex AG-50W. 120 µl of a 25% aqueous slurry of Dowex 50W is added to 96 well filter plates (0.45 µm pore size). To this is added 120 µl of terminated assay mix. 75 µl of filtrate is sampled and added to the wells of 96 well plates containing solid scintillant. After allowing the samples to dry the L-citrulline is quantified by scintillation counting.

In a typical experiment basal activity is 300 dpm per 75 µl sample of reagent controls, which is increased to 3000 dpm in the presence of enzyme. Compound activity is expressed as $IC_{50}$ (the concentration of drug substance which gives 50% enzyme inhibition in the assay) and L-NMMA, which gives an $IC_{50}$ of about 0.4 µM is tested as a standard to verify the procedure. Compounds are tested at a range of concentrations and from the inhibitions obtained $IC_{50}$ values are calculated.

In this screen the compounds of Examples 1 to 9 gave $IC_{50}$ values of less than 25 µM, indicating that they are predicted to show useful therapeutic activity.

## CLAIMS:

1. A compound of formula (I)



(I)

wherein

X represents $-[CR^6R^7]_n-$;

$R^1$ represents hydrogen or one or more substituents selected independently from C1 to 6 alkyl, C1 to 6 alkoxy, halogen and $NR^8R^9$;

$R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$ and $R^9$ independently represent hydrogen or C1 to 4 alkyl;

or $R^2$ and $R^4$ are joined together and represent $-[CH_2]_m-$;

Y represents hydrogen or C1 to 4 alkyl;

or $R^2$ and Y are joined together and represent $-[CH_2]_p-$;

or $R^4$ and Y are joined together and represent $-[CH_2]_p-$;

or Y is joined to the ortho position of ring A and represents $-[CH_2]_r-$;

Z represents a bond or $-CH_2-$;

Q represents hydrogen, C1 to 6 alkyl, C1 to 6 alkoxy, C1 to 6 alkylthio, halogen, cyano, trifluoromethyl, trifluoromethoxy, hydroxy, nitro, methanesulphonyl, sulphamoyl, benzyloxy, $-NR^8R^9$, $-CO_2R^{10}$ or $-CONR^{11}R^{12}$;

$R^{10}$, $R^{11}$ and $R^{12}$ independently represent hydrogen or C1 to 4 alkyl;

A represents phenyl, a five membered aromatic heterocyclic ring containing one or two heteroatoms selected independently from O, S or N, or a six membered aromatic azacyclic ring containing one or two nitrogen atoms;

m represents an integer 0 to 5;

n represents an integer 0 to 3;

p represents an integer 0 to 4;

r represents an integer 0 to 3;

or a pharmaceutically acceptable salt, enantiomer, racemate or tautomer thereof.

2. A compound of formula (I), according to Claim 1, wherein A represents a phenyl or pyridyl ring.

3. A compound of formula (I), according to Claim 1 or Claim 2, wherein $R^1$ represents C1 to 6 alkyl or C1 to 6 alkoxy.

4. A compound of formula (I), according to any one of Claims 1 to 3, wherein Q represents hydrogen, halogen or cyano.

5. A compound of formula (I), according to any one of Claims 1 to 4, wherein n represents 0 or 1.

6. A compound of formula (I) which is:
N-[4-(6-amino-4-methyl-2-pyridinyl)ethyl]-4-cyanobenzamide;
N-[4-(6-amino-4-methyl-2-pyridinyl)butyl]-4-cyanobenzamide;
N-[4-(6-amino-4-methyl-2-pyridinyl)ethyl]-4-chlorobenzamide;
2-[2-(6-amino-4-methyl-2-pyridinyl)ethyl]-5-bromo-2,3-dihydro-1H-isoindol-1-one;
N-[2-(6-amino-4-methyl-2-pyridinyl)ethyl]-4-cyano-N-methylbenzamide;
N-[2-(6-amino-4-methyl-2-pyridinyl)ethyl]-N-methyl-2-furanocarboxamide;
N-[2-(6-amino-4-methyl-2-pyridinyl)ethyl]-4-chloro-N-methylbenzamide;
N-[3-(6-amino-4-methyl-2-pyridinyl)propyl]-4-chlorobenzamide;
4-methyl-6-(4-(1-(4-chlorobenzoyl)piperidinyl)-2-pyridinamine;
or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

7. A compound of formula (I), according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, for use as a medicament.

8. A pharmaceutical composition comprising a compound of formula (I) according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. The use of a compound of formula (I) according to any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

10. The use as claimed in Claim 9 wherein it is predominantly inducible nitric oxide synthase that is inhibited.

11. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

12. The use as claimed in Claim 11 wherein the disease is inflammatory bowel disease.

13. The use as claimed in Claim 11 wherein the disease is rheumatoid arthritis.

14. The use as claimed in Claim 11 wherein the disease is osteoarthritis.

15. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of pain.

16. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in combination with a COX-2 inhibitor, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory diseases.

17. A method of treating, or reducing the risk of, human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial which comprises administering a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, to a person suffering from, or at increased risk of, such diseases or conditions.

18. A method of treatment according to Claim 17 in which it is predominantly inducible nitric oxide synthase that is inhibited.

19. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

20. The method of treatment as claimed in Claim 19 wherein the disease is inflammatory bowel disease.

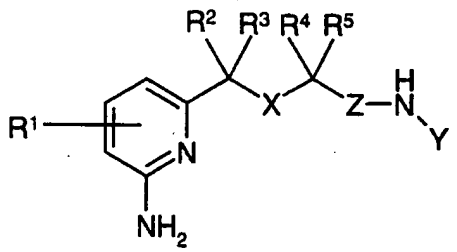
21. The method of treatment as claimed in Claim 19 wherein the disease is rheumatoid arthritis.

22. The method of treatment as claimed in Claim 19 wherein the disease is osteoarthritis.

23. A method of treating, or reducing the risk of, pain in a person suffering from, or at risk of, said condition, wherein the method comprises administering to the person a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

24. A method of treating, or reducing the risk of, inflammatory disease in a person suffering from, or at risk of, said disease, wherein the method comprises administering to the person a therapeutically effective amount of a combination of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, with a COX-2 inhibitor.

25. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 6, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein the process comprises reaction of a compound of formula (II)

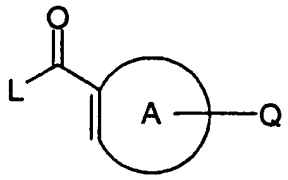



(II)

wherein

$R^1$, $R^2$, $R^3$, $R^4$, $R^5$, X, Y and Z are as defined in Claim 1

with an acyl derivative of formula (III)




(III)

wherein

Q and A are as defined in Claim 1 and L represents a leaving group;

and where desired or necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or *vice versa*, and where desired converting the resultant compound of formula (I) into an optical isomer thereof.